Original Article
Targeting protein phosphatase 2A to overcome tumor senescence in gynecologic and breast cancers

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Abstract: Protein phosphatase 2A (PP2A) is a serine/threonine phosphatase involved in a diverse array of cellular processes including mitotic progression and the DNA damage response pathway. PP2A has been classically characterized as a tumor suppressor and missense mutations affecting PP2A catalytic activity have been identified in gynecologic malignances and breast cancers. However, increasing evidence indicate that inhibition of PP2A may represent a viable strategy to overcome tumor cell senescence, a major contributor to treatment resistance after administration of conventional chemotherapies and radiation. This review overviews the tumor suppressing and tumor promoting properties of PP2A, as they pertain to the broad cancer spectrum as well as specifically to common tumors affecting women. Furthermore, therapeutic interventions targeting PP2A as a means of sensitizing tumor cells to treatment are discussed, including pre-clinical study of a novel small molecule inhibitor, LB100, currently under phase 1 clinical trial evaluation. As these studies demonstrate, PP2A represents an increasingly attractive molecular target, whose modulation may provide opportunities to overcome treatment resistance in gynecologic and breast cancers.

Keywords: Protein phosphatase 2A, cell cycle, DNA damage, gynecologic cancer, breast cancer, chemosensitization, radiosensitization

Introduction

Gynecologic malignancies and breast cancer are among the most common and devastating cancers in women. Endometrial malignancies are the most common of all gynecologic cancers worldwide with a mortality rate of approximately two persons per 100,000 women [1]. Likewise, cervical cancer affects a significant portion of the worldwide population, particularly in developing countries, where 17.8 women in 100,000 are afflicted with this disease, half of whom succumb to cancer-related deaths [2]. Ovarian cancer, while making up only 3% of cancers affecting women, remains the most deadly gynecologic cancer due to late stage diagnosis and treatment resistance [1]. On the other hand, breast cancer is the most frequently diagnosed cancer in females worldwide making up 26% of cancer diagnoses, and also contributes to 14% of all cancer-related deaths [3]. Yet despite the significant advances made and the enormous resources expended on studying these malignancies, these tumors often present at an advanced stage requiring the use of adjuvant chemo or radiation therapy [4, 5].

Great advances have been made in broad-spectrum chemotherapy and radiation as well as molecularly targeted therapies for gynecologic and breast cancers. Platinum-based chemotherapeutics among others together with radiation have demonstrated efficacy in many gynecologic cancers and have become part of many standard therapeutic regimens [6, 7]. While upwards of 75% of patients exhibit responses to these treatments, the five-year overall survivals for advanced ovarian, endometrial, and cervical cancers remain dismal at 27%, 17%, and 16%, respectively, highlighting the high rates of resistance that develop against chemo and radiation therapies [8]. For example, in ovarian cancer, primary bleomycin, etoposide, cisplatin (BEP) chemotherapy has a primary response rate of between 60-80%, but recurrent tumors tend to have drastically
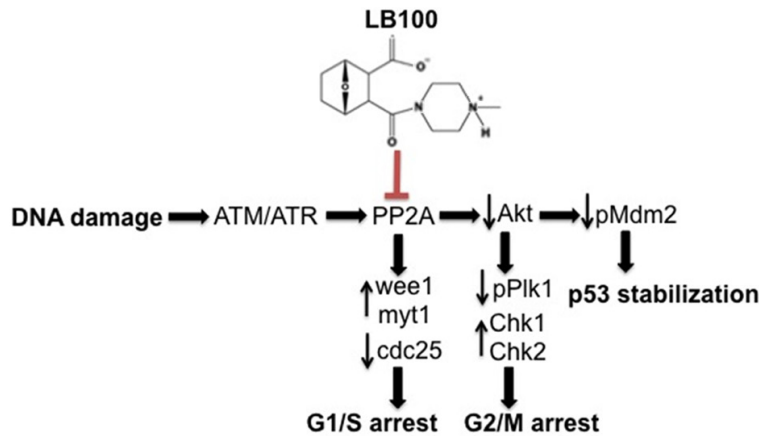
Figure 1. A simplified schematic demonstrating downstream effects of PP2A activation after DNA damage. Upwards and downwards arrows denote increases and decreases in protein activity, respectively. LB100 reverses these patterns, suppressing cell cycle arrest and stabilization of p53.

increased intrinsic resistance to cisplatin in particular, and survival after recurrence even with optimized chemotherapy and anti-VEGF therapy is generally short-lived [9]. In breast cancer, standard practice has advanced beyond conventional chemotherapeutics to include drugs targeting tumor-specific properties. Examples include trastuzumab for HER2 over-expressing tumors and hormone-regulatory therapies like the selective estrogen receptor modulator, tamoxifen, and the aromatase inhibitor, anastrozole [10, 11]. However, responses of advanced or recurrent breast cancer to these targeted therapies, even when supplemented by traditional chemotherapeutics, can be as low as 30% with response durations as low as 6 months [12, 13].

Although many mechanisms of treatment resistance exist across gynecologic and breast cancers, one common and particularly troublesome consequence is the induction of tumor cellular senescence after exposure to conventional DNA-damaging radiation and chemotherapies [14]. This has been shown in ovarian cancer, in which induction of senescence promotes resistance to paclitaxel [15]. Likewise, a unique subset of senescent breast cancer cells has demonstrated resistance to carboplatin [16]. In recent years, there has been growing interest in targeting of protein phosphatase 2A (PP2A), as a means of overcoming cell cycle arrest and induction of senescence after administration of genotoxic agents. To this end, the small mole-

cule inhibitor, LB100 (Lixte Biotechnology Holdings, Inc., East Setauket, NY), has shown promise in overcoming senescence through the inhibition of PP2A and is currently under phase 1 clinical trial investigation. In this mini-review, we overview PP2A function, as well as describe its potential applications in overcoming gynecologic and breast cancer senescence and treatment resistance. Additionally, we discuss previous work of experimental PP2A inhibition in these cancers as well as two key pre-clinical studies that demonstrated LB100 could overcome TRAIL and cisplatin resistance in breast and ovarian cancer cells, respectively.

A brief overview of PP2A functions

PP2A is a serine/threonine phosphatase, comprised of three subunits. Subunits A and C are both structural and catalytic, while subunit B serves a regulatory function [17, 18]. As a ubiquitous molecule, PP2A has many functions of interest to cancer research, including roles in mitosis, cell survival, and apoptosis. Studies in various human cancer cell lines have demonstrated that PP2A signaling plays a positive regulatory role in the Wnt/beta-catenin signal transduction pathway, promoting cell proliferation and migration [19, 20]. However, PP2A also plays a complex role in regulating cell survival or death in the context of cytotoxic stresses. ATM/ATR signaling directly activates and stabilizes PP2A through phosphorylation in response to DNA damage, leading to PP2A-mediated dephosphorylative inhibition of Akt signaling, including downregulated activity of the Akt-target MDM2. This ultimately results in phosphorylation and diminished activity of Mdm2 [21]. Phosphorylated Mdm2 is an E3 ubiquitin ligase and targets p53 for proteasomal degradation [22]. As such, activated PP2A promotes p53 stabilization via its inhibition of the Akt-Mdm2 signaling cascade [23]. Additionally, PP2A directly dephosphorylates and stabilizes p53, thereby promoting cell cycle arrest and DNA damage repair [24]. In the context of irrep-

arable DNA damage, p53 induces cell death via activation of pro-apoptotic factors such as BAX, NOXA, and PUMA. In addition to mediating cell cycle arrest through p53 activation, PP2A also suppresses cdk1-driven cell cycle progression and G1/S transition arrest [25]. Similarly, PP2A mediates G2/M arrest through inactivation of Plk1, a protein that localizes to centrosomes during mitotic spindle formation and promotes G2/M transition [26]. The downstream consequences of PP2A activation after DNA damage are illustrated in a simplified schematic (**Figure 1**).

The role of PP2A in oncogenesis

In the context of cancer research, PP2A has been classically regarded as a tumor suppressor gene. Missense mutations affecting the scaffolding A subunit of PP2A have been described in a significant proportion of gynecologic cancers, including 5-9% of low-grade ovarian carcinomas and 20-41% of high-grade endometrial serous carcinomas [27-29]. They have also been found in breast cancer, albeit at much lower frequencies [30]. The majority of these mutations have been detected in exons 5 and 6 affecting the alpha-helix structure and are postulated to alter substrate recognition and/or phosphatase activity via disruption of interaction between the A and B subunits [31, 32]. Nobumori et al. found missense mutations affecting the regulatory B subunit across a variety of human cancer cell lines, including uterine leiomyosarcoma, and demonstrated subsequent variable loss in the ability of PP2A to bind p53 [33]. Shouse et al. found similar results in lung cancer, suggesting missense mutations of the B subunit may disrupt p53-dependent tumor suppression and thus facilitate oncogenesis [34].

In further support of a tumor suppressive role for PP2A, many cancers overexpress cancerous inhibitor of PP2A (CIP2A), reviewed by De et al. [35]. CIP2A is an endogenous protein, which antagonizes PP2A-mediated ubiquitination of the proto-oncogene, c-Myc, thus stabilizing c-Myc transcriptional activity [36]. Indeed, CIP2A overexpression has been reported in 39% of breast cancers [37], 53% of cervical cancers [38], and 66% of ovarian cancers [39]. Yu et al. showed that while high levels of CIP2A were clinically correlated with increased tumor aggression in breast cancer patients, they also

predicted greater chemotherapeutic sensitivity [40]. Likewise, Laine et al. demonstrated in an *in vivo* CIP2A-deficient mouse model that xenografted breast cancer tumors became senescent and that proliferation of tumor cells was halted [41]. Taken together, these findings highlight that while CIP2A may promote deregulation of the cell cycle leading to tumor growth, CIP2A may also antagonize tumor senescence, which in the context of chemoresistant cancers, may be a desirable therapeutic strategy. Moreover, as CIP2A is an endogenous inhibitor of PP2A, these studies indirectly suggest that PP2A inhibition may render senescent tumor cells susceptible to chemotherapeutic intervention.

Inhibition of PP2A to overcome tumor senescence

Indeed, PP2A inhibition has become an increasingly tantalizing target to potentially overcome therapeutic resistance in various tumors. It is well recognized that tumor cell senescence is a major contributor to the inefficacy of conventional DNA-damaging chemotherapies and radiation that preferentially exert their cytotoxic effects upon actively dividing cells [14]. Contributing to this phenomenon is PP2A-mediated suppression of Ras signaling, which normally promotes the G2/M transition and stabilizes c-Myc [42]. In turn, the transcriptional activities of c-Myc contribute to increased cell proliferation [43]. As such, previous pre-clinical studies utilizing gynecologic and breast cancer cell lines have demonstrated that targeting PP2A activity may overcome chemoresistance. Liang et al. reported that siRNA-induced silencing of PP2A overcame Chk2-mediated cell cycle arrest in ovarian cancer cells after exposure to cisplatin and also prevented activation of other downstream players in the ATM/ATR DNA damage response pathway, including p53 [44]. McDermott et al. reported that PP2A inhibition with okadaic acid sensitized a chemoresistant HER2-positive breast cancer cell line (SKBR3-L) to HER2-targeted treatment with lapatinib [45]. Okadaic acid is a cytotoxin, naturally produced by the marine sponge, *Halichondria okadai*, with profound anti-PP2A activity [46]. It has been studied along with cantharidin, another natural compound made by the blister beetle family, as a scientific means of evaluating PP2A inhibition [47]. However, both of these compounds are highly toxic in human beings, pre-

cluding their use as pharmacologic agents [48, 49].

To circumvent the limitations of okadaic acid and the cantharidins, the small molecule LB100 (Lixte Biotechnology, Inc.) was recently developed to competitively inhibit PP2A enzymatic activity. Initially evaluated as a sensitizing agent to temozolomide in glioblastoma cells [50], the chemo-sensitizing and radio-sensitizing properties of LB100 have since been corroborated in numerous cancer types, including sarcoma [51], pheochromocytoma [52], nasopharyngeal carcinoma [53], hepatocellular carcinoma [54], and pancreatic cancer [55, 56]. Consistent with these studies, Xu et al. utilized LB100 to evaluate the efficacy of PP2A inhibition in overcoming resistance to TRAIL-mediated apoptosis in breast cancer [57]. TRAIL is a member of the tumor necrosis family and is an important initiator of the extrinsic apoptosis pathway [58]. Among other tumor types, breast cancer has been associated with TRAIL signaling resistance, contributing to both chemoresistance and tumor metastasis [59, 60]. Utilizing TRAIL-resistant BT549 breast cancer cells, Xu et al. demonstrated that TRAIL exposure led to abrogation of apoptosis via PP2A-mediated dephosphorylation of Src, a non-tyrosine kinase essential to TRAIL resistance [61]. However, treatment with LB100 overcame resistance to apoptosis after TRAIL treatment to a degree on par with the TRAIL-sensitive breast cancer cell line, MDA231.

More recently, Chang et al. studied in-depth the efficacy of LB100 in sensitizing ovarian cancer cells to cisplatin treatment [62]. This study utilized previously characterized cisplatin-resistant cell lines, SKOV-3 and OVCAR-8, in addition to patient-derived cell lines harvested both prior to and after acquisition of cisplatin resistance. The authors showed that LB100 exposure impaired activation of key DNA damage response players, including BRCA1, JNK, Chk1, and Chk2, after treatment with cisplatin. Cell cycle analysis and immunofluorescence experiments evaluating DNA damage demonstrated persistent DNA double-strand breaks, forced cell cycle progression, and resultant cell death secondary to mitotic catastrophe. *In vitro* data were confirmed *in vivo* in SKOV-3 xenografted mouse models; the addition of LB100 to cisplatin treatment slowed tumor growth five-fold without any systemic signs of toxicity, com-

pared to cisplatin administration alone. Together, these promising studies in the context of the growing LB100 literature prompted the evaluation of LB100 for human use in an ongoing phase 1 clinical trial (NCT01837667).

Conclusion

In conclusion, there is increasing evidence to support targeting of PP2A as a means of overcoming therapeutic resistance. Although classically characterized as a tumor suppressor, PP2A is becoming a molecule of interest in circumventing induction of tumor senescence in response to traditional chemotherapies and radiation, relying on active cell division. LB100 represents the first foray into treatment of human patients with targeted PP2A therapy and may yield promising options for the many suffering from treatment-resistant cancers. Regardless, accumulated data to date suggest that inhibition of PP2A represents a novel and attractive means of approaching intractable tumors and holds great potential for the future of gynecologic and breast cancer treatment.

Disclosure of conflict of interest

None.

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